

*REMARKS**The Pending Claims*

Claims 55-108 are currently pending. Reconsideration of the pending claims is respectfully requested.

*Discussion of the Claim Amendments*

Claims 55, 59, 67, 77 and 87 have been amended to recite that R may be C<sub>2</sub>-C<sub>30</sub> alkyl. Claims 56, 60, 68, 78 and 88 have been amended to recite that R may be C<sub>2</sub>-C<sub>20</sub> alkyl. Support for these amendments can be found in the application as filed, e.g., paragraphs [0032] and [0039] and in Table 1.

Claim 55 also has been amended to recite that R<sub>5</sub> and R<sub>6</sub> are C<sub>1</sub>-C<sub>8</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkenyl. Claims 63, 65, 73, 75, 83, 85, 93 and 95 have been amended to recite that R<sub>5</sub> and/or R<sub>6</sub> are a C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkenyl. Support for these amendments can be found in the application as filed, e.g., paragraph [0035].

Claims 56-58, 65, 75, 85 and 87-96 have been amended to further recite a salt of the compound. Support for these amendments can be found in the application as filed, e.g., paragraph [0070].

Claims 65, 76, 81, 82 and 97-100 have been amended to address formatting matters.

No new matter has been added by way of these amendments.

*Summary of the Office Action*

The Office Action rejects claims 99-108 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action rejects claims 55-108 under 35 U.S.C. § 112, second paragraph, for the use of an allegedly indefinite claim term.

The Office Action also rejects claims 55-58, 60, 77, 78 and 97-108 under 35 U.S.C. § 102(a) as allegedly anticipated by Bioorg. Med. Chem. *11*, 451-458 (2003) (Du et al.) (hereinafter “the Du publication”).

The Office Action further rejects claims 55, 57, 63, 97 and 99-108 under 35 U.S.C. § 102(a) as allegedly anticipated by Bioorg. Med. Chem. Lett. *13*, 3739-3741 (2003) (Pan et al.) (hereinafter “the Pan publication”).

The Office Action additionally rejects claims 55-58, 60, 77, 78 and 97-108 under 35 U.S.C. § 102(a) as allegedly anticipated by J. Org. Chem. *34* (5) 1364-1367 (1969) (Wani et al.) (hereinafter “the Wani publication”).

The Office Action rejects claims 59, 61, 62, 64-76, and 79-96 as allegedly obvious over the Du publication in view of U.S. Patents 5,968,943 and 6,407,239 (Cao et al.) (hereinafter “the Cao ‘943 patent” and “the Cao ‘239 patent,” respectively) or U.S. Patent 6,040,313 (Wall et al.) (hereinafter “the Wall ‘313 patent”).

#### *Discussion of the Enablement Rejection*

The Office Action rejects claims 99-108, directed to the use of the claimed compounds to treat cancer, under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. While the Office Action acknowledges that some of the claimed compounds have activity against a breast cancer cell line *in vitro*, it contends that this is not enough evidence of activity against other cancers to support the full scope of claims 99-108. The Office Action further alleges that there is an absence of guidance from the specification on how to use the claimed compounds against other types of cancer. In view of these alleged deficiencies, Office Action concludes that undue experimentation would be required to practice claims 99-108. Applicants respectfully traverse.

Applicants submit that the application teaches those of ordinary skill how to make and use the claimed invention. In particular, the specification offers more than enough guidance to allow those of ordinary skill to practice the claims without undue experimentation. The specification sets forth the invention such that: (1) in view of modern high throughput methods for analyzing the utility of the individual compounds (*see, e.g.*,

Sandman et al, Chemistry & Biology 6:541-51 (1999)), the quantity of experimentation necessary is not excessive for the art, (2) the amount of direction and guidance by Table 1 alone is substantial, and numerous examples teach how to make the claimed compounds, (3) more specifically, the presence of working and inoperative embodiments in Table 1 allow for the identification of structure-function relationships, (4) the chemical nature of the invention also allows for the use of structure-function correlations with prior art compounds, and (5) the level of ordinary skill in the art is quite high resulting in the use of greater insight in directing the use of the claimed compounds.

The Office Action also contends that there is no showing of the utility of the claimed compounds for treating “every type of cancer known in the art.” Office Action further contends that the specification *and the prior art* fail to teach that “camptothecin compounds “have therapeutic utility in treating every know cancer.”

On the issue of utility, a disclosure of the claimed compounds at the level required for FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use satisfies the utility requirement. MPEP § 2107.01

Moreover, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments are inoperative with the expenditure of no more effort than is normally required in the art. *See, e.g., Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). Thus, it is not necessary for all of the instantly claimed compounds to have utility in treating “every type of cancer known in the art” as the Office Action contends.

It has been long established that if an *in vitro* assay is reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. MPEP § 2107.03 III. Moreover, breast cancer and the other cancers recited by claims, as well as cancers in general, share features that can be the

targets of anti-cancer therapy, *e.g.*, abnormal DNA repair systems resulting in an increased mutation rate, resistance to apoptosis, and unchecked proliferation. Accordingly, the use of a single cancer cell line to screen antineoplastic compounds is not usual in the art. *See, e.g.*, Sandman et al, Chemistry & Biology 6:541-51 (1999). Additionally, Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound (see, *e.g.*, *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980)) and camptothecin compounds have been used to treat cancers other than breast cancer. Specification, ¶¶ [0003]-[0005].

Thus, Applicants respectfully submit that the claims are fully enabled by the application as filed, and request withdrawal of the lack of enablement rejection.

*Discussion of the Indefiniteness Rejection*

The Office Action rejects all of the pending claims (claims 55-108) under 35 U.S.C. § 112, second paragraph, for the use of the allegedly indefinite claim term “derivatives.” The Office Action points to an alleged absence of a definition for the term “derivatives” and suggests that the term be deleted from the claims. Applicants respectfully traverse.

In effect, the Office Action treats any use of the term “derivatives” as *per se* indefinite. In analyzing a claim for compliance with 35 U.S.C. 112, second paragraph, the claim as a whole must be considered to determine whether the claim apprises one of ordinary skill in the art of its scope and provides a clear warning to others as to what constitutes infringement of the patent. MPEP § 2173.02.

In the instant claims, the term “derivatives” is in the preamble and the actual subject matter of the claims, the compounds, are described fully, distinctly and concisely in the body of the claim. The structures of the claimed compounds are provided with more than adequate particularity to apprise those of ordinary skill the subject matter that the Applicants regard as their invention. Accordingly, the mere presence of the term “derivatives” in the preamble as a convenient label for the compounds described in the body of the claims in no manner renders the claims indefinite.

In view of the Office Action's failure to offer any reason why the claims, when considered as a whole, are indefinite, Applicants respectfully request withdrawal of the 35 U.S.C. 112, second paragraph, rejection.

*Discussion of the Anticipation Rejections*

Claims 55-58, 60, 77, 78, and 97-108 stand rejected as allegedly anticipated by the Du publication and the Wani publication. Both the Du and Wani publications disclose a 10, 20-diacetate derivative of 10-hydroxycamptothecin, i.e., the compound of pending claim 1 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are hydrogen and wherein R is methyl (i.e., C<sub>1</sub> alkyl). The Du publication further discloses a 7-*t*-butyldimethylsilyl-10-acetate derivative of 10-hydroxycamptothecin, i.e., the compound of pending claim 1 wherein R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub> are hydrogen, wherein R<sub>4</sub> is *t*-butyldimethylsilyl, and wherein R is methyl (i.e., C<sub>1</sub> alkyl).

As amended, claims 55-58, 60, 77, 78 and 97-108 recite a derivative of 10-hydroxycamptothecin wherein R is C<sub>2</sub>-C<sub>30</sub> alkyl or C<sub>2</sub>-C<sub>20</sub> alkyl (i.e., not C<sub>1</sub> alkyl). Accordingly, Applicants respectfully request the withdrawal of the anticipation rejection of claims 55-58, 60, 77, 78 over the Du and Wani publication.

Claims 55, 57, 63, 97 and 99-108 stand rejected as allegedly anticipated by the Pan publication. The Pan publication discloses 10-hydroxycamptothecin di(4-fluorophenoxy)acetate and 10-hydroxycamptothecin di(4-methoxyphenoxy)acetate, i.e., the compound of pending claim 1 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are hydrogen, wherein R is (CH<sub>2</sub>)<sub>n</sub>OR<sub>5</sub>, wherein n is 1, and wherein R<sub>5</sub> is C<sub>4</sub>-C<sub>10</sub> aryl.

As amended, claims 55, 57, 63, 97 and 99-108 recite a derivative of 10-hydroxycamptothecin wherein R<sub>5</sub> is not C<sub>4</sub>-C<sub>10</sub> aryl. Accordingly, Applicants also respectfully request the withdrawal of the anticipation rejection of claims 55, 57, 63, 97 and 99-108 over the Pan publication.

*Discussion of the Obviousness Rejections*

Claims 59, 61, 62, 64-76 and 79-96 stand rejected as allegedly obvious over the Du publication in view of the Cao '943 patent, the Cao '239 patent, and the Wall '313 patent.

The Office Action acknowledges that the Du publication fails to teach 10-hydroxycamptothecin derivatives wherein R is other than methyl and wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> are other than hydrogen (referring to the structure recited in pending claim 55). The Office Action relies on (a) the Cao '943 patent for its disclosure of C<sub>1</sub>-C<sub>15</sub> alkyl and C<sub>2</sub>-C<sub>15</sub> alkenyl esters at the C-20 hydroxyl group of camptothecin and C-9 substituted derivatives thereof, (b) the Cao '239 patent for its disclosure of aryl esters at the C-20 hydroxyl group of camptothecin and C-7 substituted derivatives thereof, and (c) the Wall '313 patent for its disclosure of aminoalkyl esters at the C-20 hydroxyl group of camptothecin and C-9 and C-10 substituted derivatives thereof, and asserts that it would have been obvious for one of ordinary skill in the art to modify the 10-hydroxycamptothecin 10, 20-diacetate of the Du publication with the esters disclosed in the cited publications.

The Supreme Court has instructed that in obviousness rejections that “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). While various acceptable rationales to support obviousness rejections exist, including combining prior art elements, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEPE §§ 2141 III; 2143.01. In addition, there still must be a motivation to undertake one of these actions, even if it is only based on design incentives or other market forces. *See, e.g., KSR*, 127 S.Ct. at 1742; MPEP § 2143.01.

Thus, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2142.

The Du publication discloses the 10, 20-diacetate derivatives of camptothecin and of its C-7 *t*-butyldimethylsilyl analog as synthetic intermediates but does not disclose any specific or significant utility for the disclosed intermediates. Thus, one of ordinary skill in the art would have no motivation to modify the 10, 20-diacetate derivatives of camptothecin,

much less in such a way as to arrive at the invention as recited in the pending claims, and could not have a reasonable expectation of success in doing so. See, e.g., *In re Stemniski*, 444 F.2d 581, 170 U.S.P.Q. 343, 347; *KSR*, 127 S.Ct. at 1742; MPEP § 2143.01.

The Cao '943 and '239 patents and the Wall '313 patent fail to cure the deficiencies of the Du publication. The Cao '943 patent does not disclose 10-hydroxycamptothecin derivatives, much less 10, 20-diester derivatives of 10-hydroxycamptothecin. Rather, the Cao '943 patent discloses monoester derivatives of camptothecin, which derivatives do not have a hydroxyl group at C-10 of the molecule. The Cao '239 patent and the Wall '313 patent disclose 10-*hydroxy*-20-ester camptothecin derivatives but not 10, 20-*diester* derivatives of camptothecin (see, e.g., the Cao '239 patent at col. 3, line 37, and the Wall '313 patent at col. 10, line 12). Nothing within the disclosures of the Cao '239 and Wall '313 patents teaches or suggests the desirability of modifying the disclosed camptothecin derivatives so as to arrive at the 10, 20-diester 10-hydroxycamptothecin derivatives recited in the pending claims. Absent the reliance on hindsight in view of the present application, nothing within the cited references teaches or suggests the particular 10, 20-diester 10-hydroxycamptothecin derivatives recited in the pending claims.

The Office Action has failed to set forth a case of *prima facie* obviousness. In particular, Office Action has not identified a credible reason, teaching or suggestion in any of the references to combine or modify the references to arrive at the invention as recited in the pending claims. At best, the Du publication indicates that combining prior art teachings would only yield synthetic intermediates without any specific or significant utility.

Additionally, the Office Action appears to have used Applicants' disclosure to reconstruct the invention recited in the pending claims from various references using improper hindsight.

For at least the foregoing reasons, Applicants respectfully request that the obviousness rejection of claims 59, 61, 62, 64-76 and 79-96 be withdrawn.

*Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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